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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GABEL, GAILENE	

ART UNIT	PAPER NUMBER
1641	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/827,846	EDA ET AL.	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,6,9,10,20,22 and 23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,6,9,10,20,22 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Amendment Entry

1. Applicant's amendment and response filed 7/21/03 in Paper No. 12 is acknowledged and has been entered. Claims 1, 6, 10, and 20 have been amended. Claims 5, 7, 8, 11-19, and 21 have been cancelled. Claims 22 and 23 have been added. Accordingly, claims 1-4, 6, 9, 10, 20, 22, and 23 are pending and are under examination.

Rejections Withdrawn

2. The rejections of claims 5, 7, 8, 11-19, and 21 are now moot in light of Applicant's cancellation of the claims.

3. In light of Applicant's amendment, the rejection of claims 1-3, 6, 10, and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Lindmo et al. (Journal of Immunological Methods, 126: 183-189 (1990)) is hereby, withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 20 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 20, line 2 is redundant in reciting, "have a composition have a composition".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1-4, 6, 10, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lindmo et al. (Journal of Immunological Methods, 126: 183-189 (1990)) in view of Grange et al. (Journal of Immunological Methods,1977).

Lindmo et al. teach a reagent comprising a binary mixture of microparticles having two distinguishable microparticle types. Each population of microparticles has a mean diameter and distinguishable light scattering properties, i.e. refractive index. The

first microparticle population has a mean diameter of 10 um and the second microparticle population has a mean diameter of 7um. Both microparticle types are coated with binding partners (antibody) having the same specificity but different reactivity (affinity) and have association constants of 3.2×10^{10} and 3.2×10^{9} for the 7um and 10um, respectively (see Abstract). Lindmo et al. also teach the microparticle populations as having uniform sizes at a given ratio or concentration separated by differing sizes and immunological binding partners with specific reactivities, i.e. dissociation constants, or association constants at a given ratio and concentration (see Lindmo et al., page 184-185). The microparticles are formed from polystyrene (compact styrene). The immunological binding partners are anti-CEA monoclonal antibodies (see page 184, column 2). The ratio of concentration of the first microparticles and the second microparticles in the reagent mixture are within the range of about 0.01 to about 5.0, i.e. 9×10^{6} particles/ml and 15×10^{6} (see page 185, column 2). Lindmo et al. teach that at low antigen concentrations, binding preferentially occurs on the high reactivity microparticles and the low reactivity microparticles show increase in binding with increasing antigen concentration even after binding to the high affinity particles has been saturated. This results in increase in dynamic range for an assay without compromising the high sensitivity provided by the high affinity particle (see page 184, column 2, last paragraph). Figure 2A shows a double standard curve obtained by differentially plotting the mean channel number of the fluorescence distribution for both microparticle populations as a function of antigen concentration in the sample (see page 186, second, third and fourth paragraphs). High reactivity microparticles exhibit

significant binding in comparison to low reactivity microparticles at 0.2 ug/l concentration (see Figure 2A and page 186). Lindmo et al. teach that in binary mixtures, the measurements obtained from high reactivity microparticles provide high precision in the low concentration range whereas measurements from low reactivity microparticles provide precision in the high concentration range (see page 187, second column).

Lindmo et al. differ from the claimed invention in failing to teach that the first and second microparticles have a diameter from 30 to 600 nm so as to cause light scattering at wavelengths between 300 and 1200 nm.

Grange et al. teach a reagent comprising light scattering microparticles having specific binding partners (antigens and antibodies) covalently bound thereto for use in agglutination or nephelometric assays (see Abstract). Grange et al. teach the microparticles as being 300 nm in diameter and measured at wavelengths from 220 to 600 nm. Grange et al. also teach that intensity of light scatter by a given suspension of microparticles is dependent on the size and number of the particles. Other factors that influence the intensity of light scatter includes shape, dimension, refractive index, and polydispersity of the microparticles (see page 366, last paragraph bridging to page 368). Sensitivity in agglutination assays is dependent upon the reactivity (affinity) of immunological binding partners being titered, the ratio of antigen to antibody- near equivalence, and the medium in which reaction takes place (see Introduction). According to Grange et al. light scatter is amplified by increasing "molecular size" of antigens or antibodies by adsorbing them into the microparticles with light scattering properties. In determining reactivity (specificity) between binding partners coated into

microparticles, the light scattered by microparticles which have interacted show significantly increased light scatter and is proportionate to the concentration of the antigen (see page 373).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to generate microparticles in the size range of about 300 nm as taught by Grange, into the microparticles as taught by Lindmo so as to enable detection of the microparticles in an agglutination assay because Grange specifically taught that intensity of light scatter by a given suspension of microparticles if per chance used in an agglutination assay is dependent on the size, i.e. 300 nm and number of the particles.

Lindmo et al. and Grange et al. differ from the instant invention in failing to teach that the mean diameter of the first microparticles to the mean diameter of the second microparticles ranges from about 1.5 to about 4.0 in claim 4.

However, it is maintained that mean diameters of microparticles are all result effective variables which the prior art references have shown are obtained via optimization procedures. It has long been settled to be no more than routine experimentation for one of ordinary skill in the art to discover an optimum value of a result effective variable. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum of workable ranges by routine experimentation." Application of Aller, 220 F.2d 454, 456, 105 USPQ 233, 235-236 (C.C.P.A. 1955). "No invention is involved in discovering optimum ranges of a process by routine experimentation." Id. at 458, 105 USPQ at 236-237. The "discovery of an optimum value of a result effective variable in a known process is ordinarily within the

skill of the art." Application of Boesch, 617 F.2d 272, 276, 205 USPQ 215, 218-219 (C.C.P.A. 1980). Since Applicant has not disclosed that the specific limitations recited in instant claim 4 is for any particular purpose or solve any stated problem and the prior art teaches reagents often vary according to the sample being analyzed and analyte being detected; absent unexpected results, it would have been obvious for one of ordinary skill to discover the optimum workable ranges for use of the claimed reagent disclosed by the prior art by normal optimization procedures.

6. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lindmo et al. (Journal of Immunological Methods, 126: 183-189 (1990)) in view of Grange et al. (Journal of Immunological Methods,1977) as applied to claims 1-4, 6, 10, and 20 above, and further in view of Sutton et al. (US Patent 5,330,891).

Lindmo et al. and Grange et al. have been discussed supra. Lindmo et al. and Grange et al. differ from the instant invention in failing to teach that the analyte tested for is nucleic acid and the binding partners are oligonucleotide probes.

Sutton et al. disclose microparticulate reagent for use in detecting nucleic acids wherein the microparticulates have polyoxyalkylene side chains having an oligonucleotide probe covalently attached thereto through reactive groups. The oligonucleotide probe is complementary to the nucleic acid analyte.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to covalently attach oligonucleotide probes such as taught by Sutton into the microparticles taught by Lindmo as modified by Grange in order to create a

reagent for detecting nucleic acid analytes because oligonucleotide probes constitute obvious variations of species of binding partners which are specific for nucleic acids and which are routinely varied in the art.

7. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lindmo et al. (Journal of Immunological Methods, 126: 183-189 (1990)) in view of Grange et al. (Journal of Immunological Methods,1977) as applied to claims 1-4, 6, 10, and 20 above, and further in view of Collet-Cassart et al. (US Patent 4,556,642).

Lindmo et al. and Grange et al. have been discussed supra. Lindmo et al. and Grange et al. differ from the instant invention in failing to teach that the analyte tested for is C-reactive (CRP) protein and the immunological binding partners recognize different epitopes of the CRP protein.

Collet-Cassart et al. disclose microparticles coated with immunological binding partners (anti-CRP antibodies) that recognize different epitopes of the CRP protein for use in an agglutination assay to detect CRP (see column 3, lines 44-59, Example, and claim 7.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to substitute the anti-CRP antibodies in the method of Collet-Cassart for coating into the microparticles in the method of Lindmo as modified by Granger because Lindmo specifically taught that it is well within ordinary skill to generate two groups of microparticles having distinct mean diameters coated with antibodies having distinct specificities, and Granger specifically taught that microparticles generated about

the size of 300 nm enables detection of the microparticles in an agglutination assay by virtue light scatter intensity if per chance used in an agglutination assay of a specific analyte and Collet-Cassart specifically taught application of such agglutination assay for CRP using anti-CRP antibodies coated into microparticles.

8. Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lindmo et al. (Journal of Immunological Methods, 126: 183-189 (1990)) in view of Grange et al. (Journal of Immunological Methods,1977) as applied to claims 1-4, 6, 10, and 20 above, and further in view of Kapmeyer et al. (An automated particle-enhanced nephelometric assay for the quantitative determination of PSA, Clinical Chemistry, (1996) Vol. 42, No. 6 PART 2, pp. S268-S269).

Lindmo et al. and Grange et al. have been discussed supra. Lindmo et al. and Grange et al. differ from the instant invention in failing to teach that the analyte tested for is prostate specific antigen (PSA) and the immunological binding partners recognize different epitopes of PSA.

Kapmeyer et al. et al. disclose microparticles coated with monoclonal antibodies directed against different epitopes of PSA for use in an agglutination assay to detect PSA .

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to substitute the anti-PSA monoclonal antibodies in the method of Kapmeyer for coating into the microparticles in the method of Lindmo as modified by Granger because Lindmo specifically taught that it is well within ordinary skill to

generate two groups of microparticles having distinct mean diameters coated with antibodies having distinct specificities, and Granger specifically taught that microparticles generated about the size of 300 nm enables detection of the microparticles in an agglutination assay by virtue light scatter intensity if per chance used in an agglutination assay of a specific analyte and Kapmeyer specifically taught application of such agglutination assay for PSA using anti-PSA antibodies coated into microparticles.

A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

Response to Arguments

9. Applicant's arguments with respect to the claims have been considered but are moot in view of the new grounds of rejection.

10. No claims are allowed.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday, Tuesday, and Thursday, 5:30 AM to 2:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (703) 305-3399. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-0169.

CHRISTOPHER L. CHIN
PRIMARY EXAMINER
GROUP 1800/1641

Gailene R. Gabel
Patent Examiner
Art Unit 1641
October 21, 2003